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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,006	SCHINDLER, HANSGEORG	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-45,61 and 62* is/are pending in the application.

4a) Of the above claim(s) *41 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 26-40, 42, 44, 45, 61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/10/2006 has been entered. Claims 24-45 and 61 were pending. Applicants amended claim 24, canceled claim 25 and added claim 62. Therefore, claims 24, 26-45, 61 and 62 are currently pending. Claims 41 and 43 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 24, 26-40, 42, 44, 45, 61 and 62 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. The rejection to claim 25 under 35 U.S.C. § 101 is hereby withdrawn in view of Applicant's cancellation of said claim. The rejection to claim 25 under 35 U.S.C. 112, second paragraph denoted AA is hereby withdrawn in view of Applicants' cancellation of said claim. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

3. Claims 24, 26-40, 42, 44, 45, 61 and 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

AA. Withdrawn.

BB. ***Claim 24*** recites "large-area" fluorescence excitation. The term "large-area" is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). The Examiner notes that Applicant's specification states, "Due to the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application, imaging of the excited molecules may be very rapid" (see page 7, paragraph 2). However, this statement is merely exemplary in nature and does not further limit the term "large" to a range from 100 to 10,000 μm^2 and, as a result, it is not clear to what extent the term "large" could extend beyond this limit (e.g., would 90 μm^2 infringe, 80 μm^2 infringe, etc). Thus, the metes and bounds of the claimed invention cannot be determined. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

CC. For **claim 62**, the phrase "wherein the arrangement is adapted to visualize movements of molecules ... by using the single dye tracing (SDT) method" is vague and indefinite. For example, the claimed recitation of a use (i.e., "use" of the SDT method), without setting forth any steps involved in the process (i.e., no positive method steps are set forth for the SDT method in the claim), results in an improper definition of a process

(e.g., see for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)) and, as a result, an improper definition of the apparatus that is defined (in part) by said process. Furthermore, it would appear that all of the recited elements (e.g., source of light, sample holder, etc.) could be used to monitor the movement of molecules, interactions between molecules, etc. without such an adaptation (e.g., see claim 1 of PCT/AT99/00257 priority document wherein no such "adaptation" is required for "visualizing molecules, movements thereof, and interactions between molecules, and molecular processes in a sample, in particular molecules and processes in biological cells, by using the single dye tracing"; see also specification pages 6-7). Thus, it is not clear what adaptation would be required when Applicant's priority document and specification states that no such adaptation is required.

In addition, the Schmidt et al. reference (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. "Imaging of single molecule diffusion" PNAS 1996, 93, 2926-2929) used in the 35 U.S.C. § 103(a) rejection above, according to Applicant, teaches at least one variation of the currently claimed "single dye tracing" method (e.g., see Schmidt, T. H.; Hinterdorfer, P.; Schindler, H. "Microscopy for Recognition of Individual Biomolecules" Microscopy Research and Technique **1999**, 44, 339-346, page 339, column 2, "(SDT) permits the detection and imaging of the mobility of individual biomolecules on biological membranes ... Schmidt et al. (1996a) [i.e., Applicant references the above PNAS article, used in the 35 U.S.C. §103(a) rejection as an example of an SDT method]"). However, Applicant also states that this SDT method

does not lead to the currently claimed "visualization of movements of molecules ..." (e.g., 6/27/05 Response, page 17, paragraph 1, "Schmidt [i.e., the PNAS reference above] does not teach the visualization of movements of molecules ..."). Thus, it is also unclear how the SDT method can be "used" to adapt the currently claimed arrangement for the "visualization of molecules ..." when Applicant expressly acknowledges that the SDT methods does not lead to such a result. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Response

4. Applicant's arguments directed to the above 35 U.S.C. 112, second paragraph rejections denoted BB and CC (formerly denoted A) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[BB] Applicant argues that the Examiner has not improperly "dismissed" the Declaration by Dr. Sonnleitner (e.g., see 4/10/06 Response, pages 7 and 8; see also 4/10/06 Supplemental Declaration by Dr. Max Sonnleitner under 37 C.F.R. § 1.132; see also 6/27/05 Declaration). In addition, Applicants set forth several articles by (1) Hesse-1, (2) Hesse-2 and (3) Sonnleitner and further reference the word "grobflachig" in their un-translated priority document in support of the position that "large-area fluorescent excitation" is synonymous with "wide-field illumination", which excludes the use of confocal microscopy (e.g., see 4/10/06 Response, pages 9 and 10; see also appendices; see especially page 9, first full paragraph, "large-area is used to distinguish the light source of the present arrangement from the light source used in confocal microscopy (in

which a small area is illuminated)" (internal quotations omitted)).

[CC] Applicant argues, "A recitation of a use does not automatically render a claim indefinite" and cites *Ex Parte Porter* in support of this position that the term "utilizing" is not indefinite (e.g., see 4/10/06 Response, page 10 middle paragraph).

Applicants further argue that they never expressly acknowledged that SDT methods could not be used to visualize movements of molecules, interactions between molecules and molecular processes in a sample (e.g., see 4/10/06 Response, paragraph bridging pages 10 and 11).

This is not found persuasive for the following reasons:

[BB] The Examiner has not "dismissed" either of the Sonnleitner declarations. The declarations under 37 CFR 1.132 filed on 4/10/06 and 6/27/05 are insufficient to overcome the rejection of claim 24 (and all dependent claims) based upon 35 U.S.C. 112, second paragraph as set forth in the last Office action because: The cited references (e.g., 4/10/06 Declaration, references listed on the bottom of page 2 and the top of page 3; see also appendices) fail to provide any factual basis to explain why one having ordinary skill in the art would have understood the term "large-area fluorescent excitation" to be synonymous with "wide-field illumination." Compare *In re Alton*, 76 F.3d 1168, 1179 (Fed. Cir. 1996) (the declaration offers factual evidence in an attempt to explain why one of ordinary skill in the art would have understood the specification to describe the language at issue). For example, the fact that Hesse-1 "makes frequent reference to illuminating 'large sample areas' during a process referred to as 'wide field illumination' (e.g., see 4/10/06 Response, bottom of page 9; see also Hesse-1 reference) does not

establish that "large-area fluorescent excitation" is synonymous with "wide field illumination" because the cited passages in Hesse-1 (e.g., page 310, column 1 and page 311, figure 1B and description) do not even mention the term "large-area fluorescent excitation" and thus could not possibly be used to prove its meaning. Likewise, Hesse-2 and Sonnleitner-1 also fail to even mention the term.

Furthermore, to the extent that the burden is placed on the Examiner, the Li et al. reference (e.g., see Li et al. "A new wide field-of-view confocal imaging system and its applications in drug discovery and pathology" Proc. of SPIE 2005, 6008, 1-16) is hereby set forth in support of the proposition that a person of skill in the art would understand that "large areas" can be excited using confocal imaging both by traditional methods (e.g., "tiling" procedures that add together to produce large areas) and by direct illumination using a single scan as demonstrated by Lid et al. (e.g., see Li et al., page 4, section 1.3, "The wide field-of-view confocal imaging system presented in this paper is capable of confocal imaging of large area specimen in a single scan ... without tiling, while a conventional ... confocal microscope using microscope objectives must acquire a large number of small images of the specimen, and then tile them together"). Thus, the Examiner has set forth ample evidence to cast doubt on the objective truth of Dr. Sonnleitner's statements.

[CC] The Examiner respectfully disagrees. First, *Ex Parte Porter* addressed the term "utilizing" not the currently claimed "use" language and, as a result, Applicant's arguments are moot. See, *Ex Parte Porter*, 25 U.S.P.Q.2d 1144, 1147 (Bd. Pat. App. & Inter. 1992). Second, in contrast to *Porter*, the present "use" terminology does not set

forth any "positive" method steps. For example, in *Porter* the court held, "[c]ontrary to the examiner's assertion that claim 6 has no method step, the claim clearly recites the [positive method] step of utilizing [the nozzle]." See *Id.* (internal quotations omitted). However, that is not the case here. No positive method steps can be gleaned from the phrase "using a single dye tracing (SDT) method" as recited in claim 62. For example, "use" of the single dye tracing method does not require "utilizing" any particular tangible object like the nozzle. Furthermore, MPEP § 2173.05(q) makes clear that an attempt to claim a method without setting forth positive method steps should be rejected under 35 U.S.C. 112, second paragraph (e.g., see MPEP § 2173.05(q), "Attempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph."). Consequently, any product or apparatus that is described, at least in part, by an indefinite method should also be rejected.

In addition, it has been held that the recitation that an element is "adapted to" perform a function (like in the currently claimed arrangement "adapted to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use" as recited in claim 62) is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138 (CCPA 1946). Thus, even if, *assuming arguendo*, the currently claimed "use" language did set forth a positive method step (which it does not), it would still be unclear how this method step further limits the claim because this limitation would not "constitute a limitation in any patentable sense."

With regard to the Schmidt reference, the Examiner respectfully disagrees. Applicants stated in the first full paragraph on page 17 of the 6/23/06 Response:

A key advantage of the present invention is the ability to "visualize movements of molecules, interactions between molecules, and molecular processes in a sample (claim 24) invention, Schmidt does not teach the visualization of movements of molecules, interactions between molecules, and molecular processes within a three-dimensional biological cell or cells, it only discloses artificial flat-surface lipids"

Thus, Applicant, in an attempt to distinguish claim 24 (now claim 62) and claim 25 (now canceled) admitted that Schmidt, which employs and SDT method, cannot be used to visualize the movements of molecules, interactions between molecules, and molecular processes within a three-dimensional biological cell or cells. Thus, to the extent that claim 62 encompasses the use of biological cells (i.e., the subject matter of canceled claim 25), it is not clear how an SDT method can be used to adapt such an arrangement.

Claims Rejections - 35 U.S.C. 102

5. Claims 24, 26-28, 30-34, 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharonov et al. (Sharonov, S.; Chourpa, I.; Morjani, H.; Nabiev, I.; Manfait, M. "Confocal spectral imagining analysis in studies of the spatial distribution of antitumor drugs within living cancer cells" *Analytica Chimica Acta* **1994**, *290*, 40-47) (of record).

For ***claims 24, 61 and 62***, Sharonov et al. (see entire document) disclose an apparatus for confocal spectral imaging analysis (e.g., see Sharonov et al, abstract; see

also figure 2), which anticipates claims 24 and 61. For example, Sharonov et al. disclose at least one source of light adapted to fluorescently excite, via single or multiple photon absorption marker molecules in said sample (e.g., see figure 2, element 1 wherein a Spectra-Physics Model 2026 laser is disclosed as the light source; see also abstract wherein both bound and unbound doxorubicin and mitroxantrone are disclosed and the marker molecules inside the K562 cancer cells; see also figures 4-5). Sharonov et al. do not explicitly state that the light source is configured for use in large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 34) (emphasis added). Moreover, Sharonov et al. disclose the excitation of a 20 × 20 μm region = 400 μm^2 (e.g., see Sharonov et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000 μm^2 (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below), which is between 100 to 10,000 μm^2. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and

Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection above).

In addition, Sharonov et al. disclose a sample holder (e.g., see figure 2, element 5). Sharonov et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 2, element 8). Sharonov et al. also disclose a detection and analysis system and a sample holder that are movable laterally relative to each other during use (e.g., see figure 2, elements 2 and 6; see also page 42, last paragraph, "The sample compartment is moved with an automatic scanning stage ... and can be scanned along the y-axis [i.e., laterally] with a minimum step size of 0.1 um. The scanning of the sample along the x-axis is achieved by the optical scanner being installed in the confocal entrance chamber"). Sharonov et al. also disclose a control unit that is adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system (e.g., see figure 2, elements 6 and 9; see also page 42, column 1, paragraph 2 wherein an IBM PC/AT-486 is disclosed, "The scanning of the sample stage and mirrors of the optical scanner and all operations connected with recording of spectra are computer-controlled (IBM PC/AT-486) by the ImageSoft software through the net-work between the IBM PC/AT and the RISC 6000 work station"; see also page 42, column 2, paragraphs 2-5; see also figure 3).

Sharonov et al. do not explicitly state that said arrangement has been "adapted" to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method. However,

the Examiner contends that Sharonov et al. inherently discloses this limitation (e.g., see Sharonov et al., abstract and figure 4). For example, the experimental set up in Sharonov et al. was "adapted" to visualize living cancer cells treated with the fluorescent antitumour drugs doxorubicin and mitroxantrone (e.g., see abstract). Thus, Sharonov et al. teach visualization of the movements of molecules (e.g., see Sharonov et al., page 47, "Direct express imaging of drug deposits within cells will be helpful in analyzing the accumulation [i.e., movement], distribution and efflux of the drugs"), interactions between molecules (e.g., see Sharonov et al., page, 44, paragraph bridging columns 1-2, "The fluorescence spectrum of the drug-DNA complex is changed as compared with the free drug") and molecular process in a sample during use (e.g., see page 44, paragraph bridging columns 1-2, see also figures 3-5). Furthermore, Sharonov et al. disclose the use of a "single dye" such as mitroxantrone (e.g., see figure 4) or doxorubicin (e.g., see figure 5) in each experiment. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, the Examiner argues in the alternative that Applicants' "adaptation" element (i.e., see claim 24, last three lines) represents "intended use" language and thus is

not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant's claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this "adaptation" is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph above).

For ***claim 25***, Sharonov et al. disclose an apparatus that can visualize interactions between molecules and molecular processes in biological cells (e.g., see figure 4, especially figure 4c-d wherein drug binding interactions were demonstrated for mitroxantrone in the nuclear inclusions).

For ***claim 26***, Sharonov et al. disclose "the same" marker molecules (e.g., see figure 4 wherein mitroxantrone is shown in both the nuclear membrane and in the

cytoplasm, DNA-bound mitroxantrone is also shown; see also maintained 35 U.S.C. 112, second paragraph rejection).

For ***claim 27***, Sharonov et al. disclose different marker molecules (e.g., see figure 4 wherein both "bound" and "unbound" mitroxantrone are shown; compare also figures 4-5 wherein both doxorubicin and mitroxantrone are used; see also figure 1; see also maintained 35 U.S.C. 112, second paragraph rejection).

For ***claim 28***, Sharonov et al. disclose adjusting the wavelength during use from 457.9 to 514.5 nm (e.g., see page 42, column 2, paragraph 1).

For ***claim 30***, Sharonov et al. disclose 20 μm × 20 μm = 400 μm^2 (e.g., see Sharonov et al., page 42, column 1, last paragraph).

For ***claim 31***, Sharonov et al. disclose a control unit that is adapted to coordinate and synchronize positioning and shifting of images to each sample position on a pixel array of said CCD camera (e.g., see page 41, column 2, second to last paragraph; see also page 42, column 2, paragraphs 2-3; see also page 43, column 1, paragraph 2).

For ***claims 33-34***, Sharonov et al. disclose an acousto-optically switchable laser (e.g., see figure 2, element 1; see also page 42, paragraph bridging columns 1-2 wherein a switchable Spectra-Physics Model 2026 is disclosed).

6. Claims 24, 26, 27, 30, 32, 34, 35, 37, 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie, S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, *101(38)* 7019-7023)

(10/23/03 IDS, Reference C8).

For ***claims 24 and 62***, Sanchez et al. (see entire document) disclose an apparatus for room temperature fluorescence imagining and spectroscopy of single molecules by two-photon excitation, which anticipates the claimed invention (e.g., see abstract; see also figure 1). For example, Sanchez et al. disclose at least one source of light configured for large-area fluorescence, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see figure 1 wherein Argon Ion laser is disclosed; see also Experimental section, paragraph 1 wherein a Ti-sapphire "two-photon" excitation laser is disclosed). Sanchez et al. do not explicitly state that the light source is adapted for large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claims 32 and 34; see also page 13 of Applicant's specification wherein the method of Sanchez was disclosed as a preferred embodiment) (emphasis added). Moreover, Sanchez et al. disclose the excitation of a 10 $\times$ 10 μm^2 region = 100 μm^2 (e.g., see Sanchez et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000 μm^2 (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000 μm^2, depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the

burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, Sanchez et al. disclose a sample holder (e.g., see figure 1 wherein the sample holder is labeled). Sanchez et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 1 wherein the CCD camera is labeled; see also page 7021, column 2, last paragraph; see also Experimental section wherein a Nikon Diaphot 300 inverted epifluorescent microscope is disclosed). Sanchez et al. disclose a detection and analysis system wherein at least one of the sample holder and the detection and analysis system is moveable laterally, relative to the other during use (e.g., see figure 1 wherein XY scanbed is disclosed). Finally, Sanchez et al. disclose a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use (e.g., see Experimental Section, last paragraph, wherein "a modified Nanoscope IIIA controller was used for controlling the scan bed and image acquisition"; see also figure 1).

Sanchez et al. do not explicitly state that said arrangement has been "adapted" to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method. However,

the Examiner contends that Sanchez et al. inherently discloses this limitation (e.g., see Sanchez et al., Results and Discussion; see also figure 2). For example, Sanchez et al. teach an arrangement that can image a single dye molecule (e.g., see Sanchez et al., abstract). Thus, Sanchez et al. teach the visualization of the movements of molecules (e.g., see Sanchez et al., page 7020, "Each peak in Figure 2 is due to a single molecule, evidenced by the abrupt disappearance of the signal in the subsequent images [i.e., the movement of single molecules and/or lack thereof can be ascertained via subsequent images using this technique]"), interactions between molecules (e.g., see Sanchez et al., figure 2 wherein interactions between individual RHB dye molecules and individual RHB dye molecules and the substrate surface can be seen in this and subsequent images) and molecular process in a sample during use (e.g., figure 2; see also Each peak in Figure 2 is due to a single molecule ... The variation in intensities of the molecules are due to different molecular orientations"; see also page 7019, paragraph bridging columns 1-2, "There have been tremendous developments in recent years of detection, imaging and spectroscopy of single molecules ... All these advance4s have resulted in a paradigm for studying mane single molecule behaviors , e.g., translational and rotational diffusion [e.g., examples of molecular processes] ... etc."). Furthermore, Sanchez et al. disclose the use of a single dye tracing method (e.g., see Sanchez et al., abstract, "We report fluorescence imaging of single dye molecules ...")."When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make

such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, the Examiner argues in the alternative that Applicants' "adaptation" element (i.e., see claim 24, last three lines) represents "intended use" language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant's claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this "adaptation" is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. §

112, second paragraph below).

For ***claim 26***, Sanchez et al. disclose, for example, "the same" RhB dye marker molecules (e.g., see Figure 2)

For ***claim 27***, Sanchez et al. disclose do not disclose the use of "different marker molecules, but this limitation has not been given any patentable weight because it represents intended use only. If the prior art structure is capable of performing the intended use, then it meets the claim. The Office does not have the facilities to make a comparison and the burden is on the applicants to establish any difference between the transducing elements of the art and the instant claims. Se In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 30***, Sanchez et al. disclose $10 \times 10\ \mu m = 100\ \mu m^2$ (e.g., see Sanchez et al. page 7022, column 2, paragraph 1).

For ***claims 32 and 34***, Sanchez et al. disclose, for example, an argon laser and/or a "two-photon" excitation laser (e.g., see figure 1; see also Experimental section).

For ***claim 35***, Sanchez et al. disclose a control unit that further comprises a pulse transmitter and a software adapted to control said at least one source of light and said movement of said sample holder during use (e.g., see Sanchez et al., figure 1; see also Experimental section, paragraph 3, wherein Nanoscope IIIA controller is used for "controlling the scan bed and image acquisition"; see also paragraph 1 wherein 100 fs pulses are disclosed).

For ***claim 37***, Sanchez et al. disclose an inverted epifluorescence microscope

(e.g., see Experimental section).

For ***claim 61***, Sanchez et al. disclose lateral movement (e.g., see figure 1, XY scanbed).

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicant argues, "Sharonov and Sanchez do not teach 'a light source configured for use in large-area fluorescent excitation' ... The fact that Sharonov and Sanchez are directed solely to confocal microscopy is precisely the reason that Sharonov and Sanchez do not anticipate the present claims, as confocal microscopy is completely different from the large-area fluorescent excitation technique taught by the present claims" (e.g., see 4/10/06 response, pages 11-14). In addition, Applicants further explain the different between large-area fluorescent excitation, which the equate with wide-field illumination, and confocal microscopy, which they equate with "small area" excitation (e.g., see 4/10/06 response, pages 12 and 13). Applicants then conclude by stating "Light sources, such as lasers, that are configured for use in confocal microscopy simply will not work for large-area fluorescent excitation" (e.g., 4/10/06 Response, page 14, middle paragraph).

[2] Applicant argues, "Sharonov and Sanchez do not teach 'a control unit adapted to coordinate and synchronize illumination times and lateral movement' ... A disclosure that

scanning operations are 'computer-controlled' [referring the Sharonov] does not amount to the teaching of a controller adapted to coordinate and synchronize illumination times and lateral movement ... [Similarly] [t]he disclosure that a 'controller' [referring to Sanchez] was used for controlling the scan ed and image acquisition does not amount to the teaching of a controller adapted to coordinate and synchronize illumination times and lateral movement" (e.g., see 4/10/06 Response, pages 14-16, section 2.).

[3] Applicant argues, "Sharonov and Sanchez do not teach 'wherein the arragnemnt is adapted to visualize movements of molecules ... by using a single dye tracing (SDT) method' ... As stated in the Sonnleitner Declaration attached to the previous Response, Sharonov teaches nothing about SDT. SDT is a technique that combines molecular recognition by antibodies or ligands with time-resolved fluorescence microscopy of single fluorophores for the study of single biomolecules in physiological environments or in isolation, with information about position, motion, conformational transitions, associations and stoichiometries. Merely disclosing the use of a 'single dye' in an experiment does not amount to a teaching of the particular technique known as SDT" (e.g., see 4/10/06 Response, page 16, last paragraph; see also page 17, paragraphs 1 and 2; see also Dr. Sonnleitner's declarations). Applicants further state that the Action's "alternative" argument because clear structural limitations have been set forth (e.g., see 4/10/06 Response, page 17).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. The metes and bound of the term "large-area fluorescent excitation" is not clear (e.g., see 35 U.S.C. 112, second paragraph) and, as result, Applicants' arguments are moot. Furthermore, Li et al. clearly demonstrate that "large areas"

can be excited using confocal microscopy using both a "single scan" and a "tiling process" (e.g., see Li et al., page 4, section 1.3, "The wide field-of-view confocal imaging system presented in this paper is capable of confocal imaging of large area specimen in a single scan ... without tiling, while a conventional ... confocal microscope using microscope objectives must acquire a large number of small images of the specimen, and then tile them together"). Since "large area" fluorescent excitation does not require the use of "simultaneous" excitation, both the "single scan" and the "tiling process" would read on Applicant's claims. Claims are to be given their broadest reasonable interpretation consistent with Applicants' specification (e.g., see *In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111.

[2] It has been held that the recitation that an element is "adapted to" perform a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138 (CCPA 1946). Consequently, Applicants arguments are moot because Applicant's use of "adapted to" in the disputed phrase "adapted to coordinate and synchronize illumination times and lateral movement between said sample hold and said detection and analysis system during use" does not constitute a "limitation in any patentable sense" in accordance with *In re Hutchinson.* In addition, the terms "coordinate" and "synchronize" represent mere "intended use" language and thus are not afforded any patentable weight. A statement of intended use does not qualify or distinguish the structural apparatus claimed over the reference. *In re Sinex*, 309 F.2d 488, 492, 135 USPQ 302, 305 (CCPA 1962). The manner or method in which a machine is to be utilized is not germane to the issue of patentability of the machine itself. See In re Casey, 370 F.2d 576, 580, 152 USPQ

235, 238 (CCPA 1967); *In re Yanush*, 477 F.2d, 958, 959, 177 USPQ 705, 706 (CCPA 1973).

Alternatively, to the extent that the disputed phrase can be regarded as a patentable limitation (*assuming arguendo*), the Examiner contends that both Sanchez and Sharonov explicitly or inherently disclose Applicant's disputed limitation. For example, Sharonov et al. disclose a control unit that is adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system (e.g., see figure 2, elements 6 and 9; see also page 42, column 1, paragraph 2 wherein an IBM PC/AT-486 is disclosed, "The scanning of the sample stage and mirrors of the optical scanner and all operations connected with recording of spectra are computer-controlled (IBM PC/AT-486) by the ImageSoft software through the net-work between the IBM PC/AT and the RISC 6000 work station"; see also page 42, column 2, paragraphs 2-5; see also figure 3). Likewise, Sanchez et al. disclose a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use (e.g., see Experimental Section, last paragraph, wherein "a modified Nanoscope IIIA controller was used for controlling the scan bed and image acquisition"; see also figure 1).

Finally, the Examiner notes that while the specification sets forth that the control unit "may" be effected by the CCD camera itself or by a pulse transmitter and a software for controlling the source of light and the (relative) movement of the sample (e.g., see specification, page 8, last paragraph), none of these examples are required (e.g., see paragraph bridging pages 8 and 9, "Such control may [i.e., it is not required], e.g., be effected by the CCD camera [i.e., merely an example] itself or by an arrangement comprising a pulse transmitter and a software for controlling the source(s) of light and the (relative) movement of the sample [i.e.. merely another

example]. In this instance, preferably [i.e., is not required], the control unit can also coordinate and synchronize the positioning and the shifting of the images to each sample position on the pixel array of the CCD camera and control and coordinate the readout and the evaluation of the pixel array images [i.e., merely an example]"). Thus, the claims are not limited to the specific embodiments referred to by Applicants (e.g., see 4/10/06 Response, page 15, paragraph 1).

[3] The phrase "wherein the arrangement is adapted to visualize movements of molecules ... by using the single dye tracing (SDT) method" in claim 62 is vague and indefinite and, as a result, Applicants' arguments are moot (e.g., see 35 U.S.C. 112, second paragraph rejection above). In addition, it has been held that the recitation that an element is "adapted to" perform a function (like in the currently claimed arrangement "adapted to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use" as recited in claim 62) is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138 (CCPA 1946). Thus, even if, *assuming arguendo*, the currently claimed "use" language did set forth a positive comprehensible limitation (which it does not), it would still fail to "constitute a limitation in any patentable sense" in accordance with *In re Hutchison.*

Alternatively, to the extent that the disputed phrase can be regarded as a patentable limitation (*assuming arguendo*), the Examiner contends that both Sanchez and Sharonov explicitly or inherently disclose Applicant's disputed limitation. For example, the experimental set up in Sharonov et al. was "adapted" to visualize living cancer cells treated with the fluorescent antitumour drugs doxorubicin and mitroxantrone (e.g., see abstract). Thus, Sharonov et al. teach visualization of the movements of molecules (e.g., see Sharonov et al., page 47,

"Direct express imaging of drug deposits within cells will be helpful in analyzing the accumulation [i.e., movement], distribution and efflux of the drugs"), interactions between molecules (e.g., see Sharonov et al., page, 44, paragraph bridging columns 1-2, "The fluorescence spectrum of the drug-DNA complex is changed as compared with the free drug") and molecular process in a sample during use (e.g., see page 44, paragraph bridging columns 1-2, see also figures 3-5). Furthermore, Sharonov et al. disclose the use of a "single dye" such as mitroxantrone (e.g., see figure 4) or doxorubicin (e.g., see figure 5) in each experiment. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Thus, it is Applicant's burden to show that the prior art is not the same. This has not been done.

Likewise, Sanchez et al. teach an arrangement that can image a single dye molecule (e.g., see Sanchez et al., abstract). Thus, Sanchez et al. teach the visualization of the movements of molecules (e.g., see Sanchez et al., page 7020, "Each peak in Figure 2 is due to a single molecule, evidenced by the abrupt disappearance of the signal in the subsequent images [i.e., the movement of single molecules and/or lack thereof can be ascertained via subsequent images using this technique]"), interactions between molecules (e.g., see Sanchez et al., figure 2 wherein interactions between individual RHB dye molecules and individual RHB dye molecules and the substrate surface can be seen in this and subsequent images) and molecular process in a sample

during use (e.g., figure 2; see also Each peak in Figure 2 is due to a single molecule ... The variation in intensities of the molecules are due to different molecular orientations"; see also page 7019, paragraph bridging columns 1-2, "There have been tremendous developments in recent years of detection, imaging and spectroscopy of single molecules ... All these advance4s have resulted in a paradigm for studying mane single molecule behaviors , e.g., translational and rotational diffusion [e.g., examples of molecular processes] ... etc."). Furthermore, Sanchez et al. disclose the use of a single dye tracing method (e.g., see Sanchez et al., abstract, "We report fluorescence imaging of single dye molecules ...")."When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

The declarations under 37 CFR 1.132 filed on 4/10/06 and 6/27/05 are insufficient to overcome the rejection of claims 24, 26-28, 30-34, 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharonov et al. and 24, 26, 27, 30, 32, 34, 35, 37, 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanchez et al. as set forth in the last Office action because: (1) the disputed claim language is unclear (e.g., see 35 U.S.C. 112, second paragraph), (2) the "adapted to" language does not constitute a patentable limitation in accordance with *In re Hutchison*, 69 USPQ 138 (CCPA 1946) (see above) and (3) Applicants' have not refuted the

inherency argument set forth above in accordance with In re Spada (see above).

Accordingly, the 35 U.S.C. §102(b) rejections cited above are hereby maintained.

Claim Rejections - 35 USC § 103

8. Claims 24, 26, 27, 29, 30, 32, 34, 35, 37, 44, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie, S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, *101(38)* 7019-7023) (10/23/03 IDS, Reference C8) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**).

For ***claims 24, 26, 27, 30, 32, 34, 35, 37, 61 and 62***, Sanchez et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 24, 26, 27, 30, 32, 34, 35, 37, 61 and 62.

The prior art teaching of Sanchez et al. differs from the claimed invention as follows:

For ***claim 29***, the prior art teachings of Sanchez et al. differ from the claimed invention by not specifically reciting the use of both horizontal (x an y direction) and vertical (z direction) control.

For ***claim 44***, the prior art teachings of Sanchez et al. differ from the claimed invention by not reciting the use of a piezo element.

However, Lewis et al. teach the following limitations that are deficient in Sanchez

et al.:

For ***claim 29***, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For ***claim 44***, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously").

It would have been obvious to one skilled in the art at the time the invention was made to use the fluorescence imaging and spectroscopy apparatus as taught by Sanchez et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their "flat design" is "particularly well suited for ... confocal optical microscopy" (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Sanchez et al. (e.g., see Sanchez et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state that their invention is "ideally suited for stage scanning confocal optical microscopy. Its inherent axial positioning capability provides a mechanism for optically slicing s ample in the z direction while scanning it through the confocal spot" (e.g., see

Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4, "The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes and especially with confocal microscopy disclosed by Sanchez (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

Response

9. Applicant's arguments directed to the above Sanchez 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) rejections were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejections have been modified from their original version to more clearly address applicant's newly amended and/or added claims and/or arguments.

Applicant argues, "[a]s explained in detail above ... ." (e.g., see 4/10/06 Respsone, page 18, paragraphs 1 and 2).

This is not found persuasive for the following reasons:

To the extent that Applicant is merely repeating his previous arguments, the Examiner contends that those issues were adequately addressed in the previous sections (e.g., see above), which are incorporated in their entirety herein by reference.

Accordingly, the Sanchez et al. 35 U.S.C. § 103(a) rejections cited above are hereby maintained.

10. Claims 24, 26-40, 42, 44, 45, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. "Imaging of single molecule diffusion" PNAS 1996, 93, 2926-2929) (of record) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**) as evidenced by Schmidt et al. (Schmidt, T. H.; Hinterforfer, P.; Schnidler, H. "Microscopy for Recognition of Individual Molecules" *Laser und Optoelektronik* **1997**, *29(1)*, 56-62) (referred to herein as "Schmidt 1997") and Albertine et al. (e.g., see Albertine, K. H.; Cerasoli, F.; Gee M. H.; Ishihara, Y.; Tahamont, M. V.; Gottlieb, J. E.; Peters, S. P. "Morphological analysis of the activation of adherent neutrophils in vitro" *Tissue Cell* **1998** *20(4)*, 519-530) and Al-Ghoul et al. (Al-Ghoul, K. J.; Costello, M. J.; "Light Microscopic Variation of Fiber Cell Size, Shape and Ordering in the Equatorial Plane of Bovine and Human Lenses" Molecular Vision 1997, 3, 2).

For ***claims 24 and 62***, Schmidt et al. (see entire document) teach a method for imaging single molecule diffusion (e.g., see Schmidt et al., abstract), which reads on the claimed invention. For example, Schmidt et al. teach the use of at least one source of light configured for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see Schmidt et al., page 2926 wherein an argon-laser is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also figure 1). In addition, Schmidt et al. teach a sample

holder (e.g., see page 2927, column 1, paragraph 2 wherein samples are immobilized on a cover-slip). Schmidt et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see Schmidt et al., page 2926 wherein an epifluorescence microscope equipped with a nitrogen-cooled CCD camera is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"). Finally, Schmidt et al. disclose a control unit adapted to coordinate and synchronize illumination times (e.g., see Schmidt et al., page 2926-2927 wherein a CCD camera equipped with a TH512B chip is disclosed "... provid[ing] trigger pulses for the acousto-optic modulator for repeated illuminations"). Schmidt et al. also disclose an arrangement adapted to visualize movements of molecules, interactions between molecules, and molecular process in a sample during use (e.g., see Schmidt et al., abstract, "Here we provide methodology for visualization of the motion of individual fluorescent molecules"; see also figures 1 and 3 showing interaction of individual lipid with other lipids in the membrane).

In addition, the Examiner argues in the alternative that Applicants' "adaptation" element (i.e., see claim 24, last three lines) represents "intended use" language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). "[A]pparatus claims cover what a device is, not what a device does." *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A

claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus" if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant's claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this "adaptation" is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph below).

For ***claim 25***, Schmidt et al. disclose the use of biological cells (e.g., see Schmidt et al., page 2929, Conclusion).

For ***claims 26-27***, a recitation directed to the manner in which a claimed apparatus is intended to be used does not distinguish the claimed apparatus from the prior art – if the prior art has the capability to so perform. See MPEP 2114 and *Ex parte Masham*, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicants use of equal or different markers does not impart any patentably distinct features on the apparatus and thus is not given any patentable weight in accordance with MPEP § 2114. However, even if assuming arguendo the use of said sample markers were to be given patentable weight, Schmidt et al. disclose both equal and different marker molecules (e.g., Materials and Methods section wherein equal TRITC DHPE molecules are disclosed; see also bell

curve in figure 2 showing some "markers" with less than 100 counts and some with greater than 300 counts i.e., different markers; see also Conclusion wherein different markers are disclosed).

For ***claim 28***, Schmidt et al. disclose the coordination and synchronization of 5 ms Gaussian-shaped laser beam pulses of 6.1 μm width and 57 kW/cm2 mean excitation intensity taken at 35 ms intervals (e.g., see figures 1 and 3).

For ***claim 30***, Schmidt et al. do not explicitly state that their laser will excite a range from 100 to 10,000 μm^2, but the Examiner contends that this level of excitation would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 32) (emphasis added). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

For ***claim 31***, Schmidt et al. disclose positioning and shifting of images using a "frameshift" CCD camera equipped with both (1) acquisition and (2) storage functional

capabilities and the ability to "synchronize" and "coordinate" between these two functions.

For ***claims 32 and 34***, Schmidt et al. disclose an argon-ion laser (e.g., see Schmidt et al., page 2926, column 1, paragraph 1).

For ***claim 33***, Schmidt et al. disclose an acousto-optically switchable laser light (e.g., see Schmidt et al., page 2927, column 1, paragraph 1, "The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations").

For ***claim 35***, Schmidt et al. disclose a pulse transmitter and mechanism for controlling said transmitter wherein the laser can generate 5 ms pulses (e.g., see Schmidt et al., Materials and Methods section; see also page 2927, column 1, paragraph 1, "The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations").

For ***claim 36***, Schmidt et al., disclose both "continuous" and "frameshift" CCD modes (e.g., see Schmidt et al., page 2926, column 2, last paragraph).

For ***claim 37***, Schmidt et al., disclose an epifluorescence microscope (e.g., see page 2926, column 1, last paragraph, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also Materials and Methods section).

For ***claim 38***, Schmidt et al. disclose and efficiency of 3% (e.g., see Schmidt et al., page 2926, column 1, last paragraph).

For ***claim 39***, Schmidt et al. disclose a N_2 cooled CCD camera with a large pixel array and noise of only a few electrons per pixel (e.g., see page 2926, column 1, last

paragraph, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also Materials and Methods section wherein 4 counts/pixel read-out noise is disclosed). Schmidt et al. do not disclose the quantum efficiency or dark counts of their SDT system. The reference is silent on the issue. However, the Examiner contends that these features would be an inherent property of the system as disclosed by a later paper by Schmidt et al. (referred to herein as "Schmidt 1997") referring back to the previous studies (e.g., see Schmidt 1997, translation, page 7, Figure 1B shows the setup for single molecule detection with a conventional epifluorescence microscope and a nitrogen-cooled CCD camera (4cnts readout noise, dark counts negligible, quantum efficiency 0.8 electrons/photon)"; please note that reference [12] refers to the previous Schmidt et al. article published in 1996).

For ***claim 45***, Schmidt et al discloses the same Axiovert 135-TV Zeiss microscope as that disclose in Applicant's preferred embodiments (e.g., see Example 1 in Specification) and, as a result, must possess the same parallel beam region. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Schmidt et al. differ from the claimed invention as

follows:

For ***claims 29 and 35***, Schmidt et al. are deficient in that they do not specifically teach the use of an XYZ stage for automated lateral and vertical movements. Schmidt et al. is silent on the issue.

For ***claim 40***, Schmidt et al. are deficient in that they do not teach the use of a pixel array > 1340 × 1300.

For ***claim 42***, Schmidt et al. are deficient in that they do not teach the use of a microtiter plate.

For ***claim 44***, Schmidt et al. are deficient in that they do not teach the use of a piezo element used in conjunction with the XYZ stage for Z moments.

However, the combined references of Lewis et al., Al-Ghoul et al. and Albertine et al. teach the following limitations that are deficient in Schmidt et al.:

For ***claims 29 and 35***, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For ***claim 40***, Al-Ghoul et al. teach the use of a pixel array that is 2048 × 2048 (e.g., see page 2, column 2, paragraph 2).

For ***claim 42***, Albertine et al. teach the use of a microtiter plate for use in microscopy of biological samples for "parallel" screening and identification (e.g., see

Albertine et al., abstract).

For ***claim 44***, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously").

It would have been obvious to one skilled in the art at the time the invention was made to use the single dye tracing apparatus as taught by Schmidt et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their "flat design" is "particularly well suited for ... microscopy" (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Schmidt et al. (e.g., see Schmidt et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state, "The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective" (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4), which would encompass the microscope objective disclosed by Schmidt et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the

plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

In addition, a person of skill in the art would have been motivated to use the microtiter plates disclosed by Albertine et al. with the single dye tracing apparatus as disclosed by Schmidt et al. because Albertine et al. explicitly states that their microtiter plates can be used with microscopy (e.g., see Albertine et al., abstract). Furthermore, a person of skill in the art would have been motivated to use a microtiter plate to prepare and/or test samples in "parallel" i.e., to save time. Furthermore, a person of skill in the art would have reasonably been expected to be successful because Albertine et al. show that microtiter plates can be used in conjunction with microscopes.

Finally, a person of skill in the art would have been motivated to use the 2048 × 2048 pixel array to replace the smaller arrays disclosed by Schmidt et al. because this array is designed to collect images in the same manner as the smaller arrays (i.e., the references represent analogous art). A person of skill in the art would have been motivated to use the array disclosed by Al-Ghoul et al. because it possesses higher resolution (i.e., 2048 × 2048). A person of skill would have reasonably been expected to be successful because the array is used in a CCD camera just as is the case for Schmidt et al.

Response

11. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed

persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues, "Schmidt does not teach a control unit adapted to coordinate and synchronize illumination times and lateral movement between a sample holder and a detection and analysis system during use. In fact, the Action does not even assert that Schmidt teaches a control unit adapted to coordinate and synchronize illumination times and lateral movement, instead merely arguing that Schmidt teaches a 'control unit adapted to coordinate and synchronize illumination times' ... The control unit of the present claims allows one to synchronize the lateral movement of the stage in scanning direction with the readout of the camera. Each time a camera line is readout ... the control unit triggers the stage to move the sample exactly the distance corresponding to the camera pixel size divided by the magnification of the microscope objective ... this means that the electrons generated by the photons emitted by one fluorophores are transported along the camera chip with the same velocity as the fluorophores in the sample that is moved by the stage" (e.g., see 4/10/06 Response, pages 19 and 20).

This is not found persuasive for the following reasons:

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., control unit triggers the stage to move the sample exactly the distance corresponding to the camera pixel size divided by the magnification of the microscope objective; control unit drives the stage in a quasi-continuous motion; photons emitted by one fluorophores are integrated on the camera chip; etc.)

are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

It has been held that the recitation that an element is "adapted to" perform a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138 (CCPA 1946). Consequently, Applicants arguments are moot because Applicant's use of "adapted to" in the disputed phrase "adapted to coordinate and synchronize illumination times and lateral movement between said sample hold and said detection and analysis system during use" does not constitute a "limitation in any patentable sense" in accordance with *In re Hutchinson*. In addition, the terms "coordinate" and "synchronize" represent mere "intended use" language and thus are not afforded any patentable weight. A statement of intended use does not qualify or distinguish the structural apparatus claimed over the reference. *In re Sinex*, 309 F.2d 488, 492, 135 USPQ 302, 305 (CCPA 1962). The manner or method in which a machine is to be utilized is not germane to the issue of patentability of the machine itself. See In re Casey, 370 F.2d 576, 580, 152 USPQ 235, 238 (CCPA 1967); *In re Yanush*, 477 F.2d, 958, 959, 177 USPQ 705, 706 (CCPA 1973).

Alternatively, to the extent that the disputed phrase can be regarded as a patentable limitation (*assuming arguendo*), the Examiner contends that Schmidt explicitly or inherently disclose Applicant's disputed limitation. For example, Schmidt et al. disclose a control unit adapted to coordinate and synchronize illumination times (e.g., see Schmidt et al., page 2926-2927 wherein a CCD camera equipped with a TH512B chip is disclosed "... provid[ing] trigger pulses for the acousto-optic modulator for repeated illuminations"; see also 35 U.S.C. 112,

second paragraph rejection below). Schmidt et al. also disclose an arrangement adapted to visualize movements of molecules, interactions between molecules, and molecular process in a sample during use (e.g., see Schmidt et al., abstract, "Here we provide methodology for visualization of the motion of individual fluorescent molecules"; see also figures 1 and 3 showing interaction of individual lipid with other lipids in the membrane).

Finally, the Examiner notes that the specification sets forth that the control unit "may" be effected by the CCD camera itself i.e., without the use of software for controlling the lateral movement of a stage (e.g., see paragraph bridging pages 8 and 9, "The control unit of the arrangement according to the invention serves to coordinate and synchronize the illumination times and ... also to coordinate the lateral or vertical relative movements between sample and detection and analysis system. Such control. may ... be effected by the CCD camera itself or by an arrangement comprising ... software for controlling the source(s) of light and the (relative) movement of the sample"). Thus, the claimed control unit does not even require controlling the sources of light and the relative movement of the sample as purported (e.g., see 4/10/06 Response, page 19, last paragraph). Consequently, Applicant's arguments (e.g., see 4/10/06 Response, pages 19 and 20) are not commensurate in scope with the claims.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 24, 26-40, 42, 44, 45 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claim 24 was amended in the 4/10/06 Response. However, applicant did not show where support for these amendments and/or deletions can be found in the specification. Specifically, to the extent that the deletion of the phrase "wherein the arrangement is adapted to visualize movements of molecules ... using a single dye tracing (SDT) method" increases the scope of the claims (i.e., the claim is not longer limited to SDT adaptation), the increased breadth represents new matter. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02. Therefore, claim 24 and all dependent claims are rejected for containing new matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
June 25, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER